REMARKS

Claims 1, 3-4, 8, and 11-12 have been amended to clarify that the protease inhibitor is an HIV protease inhibitor. New claim 37 has been added to specify that the antiviral protease inhibitor is an HIV protease inhibitor. No new matter is added by way of these amendments.

The specification stands objected to and claims 1-2, 5-15, and 18-22 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to provide information allowing the skilled artisan to practice the present invention without undue experiment, and thereby failing to provide an enabling disclosure. The Examiner contends that only a limited number of compounds are set forth in the specification for "protease inhibitors," thereby failing to provide sufficient working examples.

Both the specification and claims in the present invention teach treatment of HIV infection by co-administering a compound of Formula I or II and an HIV protease inhibitor. Thus, while the term "protease inhibitor" is used, this term is used throughout the specification to refer to various "HIV protease inhibitors." (See, e.g., page 1, line 9; page 6, line 31 to page 7, line 8 (discussing various known HIV protease inhibitors); page 7, line 19, etc.). As filed, claim 1 specified "HIV protease inhibitor" in lines 1-2 and claim 2 specifically refers to an "HIV protease inhibitor". Claims 1, 3-4, 8, and 11-12 have been amended to clarify that the protease inhibitor is an "HIV protease inhibitor."

The group of "HIV proteases inhibitors" is not an unduly large class of compounds and the presently claimed invention does not require undue experimentation. Furthermore, various incorporated references provide definition for the term "HIV proteases inhibitors." For example, References AR and AW of the January 22, 2002 Information Disclosure Statement, and References AC and AD of the May 2, 2002 Information Disclosure Statement all teach various HIV protease inhibitors as a class and by activity in inhibiting the HIV-1 protease enzyme. The specification also teaches various members of this class, for example on page 6, line 31 to page 7, line 8, as well as in claims 3 and 16. Applicants respectfully submit that the class of HIV protease inhibitors is not so broad as to require undue experimentation. Similarly, claims 13-15 and 18-22 specify that the protease inhibitor is an antiviral protease inhibitor. While larger than the class of HIV protease inhibitors, the class of antiviral protease inhibitors is much more limited than the class of all protease inhibitors. Accordingly, applicants respectfully request withdrawal of the objection to the specification and rejection of claims 1-2, 5-15, and 18-22 under 35 U.S.C. § 112, first paragraph.

Second, claims 1-2, 5-15, and 18-22 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that the phrase "protease inhibitors" renders these claims indefinite and thereby failing to clearly set forth the metes and bounds of the present invention.

As discussed above, claims 1-2 and 5-12 have been amended to clarify that the protease inhibitor is an HIV protease inhibitor. Similarly, claims 13-22 do not require any protease inhibitor, as suggested by the Examiner, but instead require an antiviral protease inhibitor. Thus, applicants submit that the claims point out and distinctly claim the invention. Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Finally, the examiner has rejected claims 1-22 under 35 U.S.C. § 103(a) as being obvious over Kim et al. (J. Clinical Investigation, vol. 101(2), Jan. 1998, pages 187-88) in view of Pfister et al. (U.S. Patent No. 5,654,304). The examiner asserts a *prima facie* obvious case for the mere concomitant employment of an efficacious anti-retroviral therapeutic agent and conventional P-glycoprotein inhibiting agents from the two cited references.

While various P-glycoprotein inhibiting agents are known, many are known to interact with drug metabolizing enzymes, in particular, members of the cytochrome P4503A subfamily (CYP3A). Because many P-glycoprotein inhibitors also inhibit CYP3A and vice-versa, use of P-glycoprotein inhibitors is associated with increased plasma levels of the CYP3A substrate. Thus, at the time this invention was made, it was known that many P-glycoprotein inhibitors result in system toxicity. Furthermore, in the last sentence of Kim et al., the authors address the concern of *in vivo* application because of potential inhibition of the metabolism of HIV protease inhibitors to alter their systemic availability and elimination characteristics. Thus, Kim et al. in fact teaches away from a reasonable expectation of success by suggesting potential difficulties. Because the prior art is replete with the difficulties associated with the use of P-glycoprotein inhibitors, when taken as a whole, the prior art does not suggest the use of any particular P-glycoprotein inhibitor in combination with HIV protease inhibitors, and certainly not the compounds of Formulae I and II in combination with HIV protease inhibitors.

Respectfully, the present specification emphasizes the distinct property of claimed methanodibenzosuberane compounds having P-glycoprotein transporter inhibition with minimal effect on CYP3A (Specification page 9, line 5-20). The minimal effect on

CYP3A is not suggested or taught by either Kim et al. or Pfister et al. Furthermore, as shown in Fig. 3, the compound of Formula II is actually more effective than various other known P-glycoprotein inhibitors in increasing the concentration of an HIV protease inhibitor, nelfinavir, in both the testes and brain. Similar results were achieved with saquinavir and indinavir. Thus, the co-administration of the compound of Formula II and an HIV protease inhibitor show synergistic effects that were not obvious from the prior art. Accordingly, applicants respectfully submit that at the time the invention was made, the claimed combination was not obvious over Kim in view of Pfister. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

The application is believed to be in condition for allowance. Withdrawal of the rejection and passage of the application to issuance is respectfully requested.

Respectfully submitted,
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